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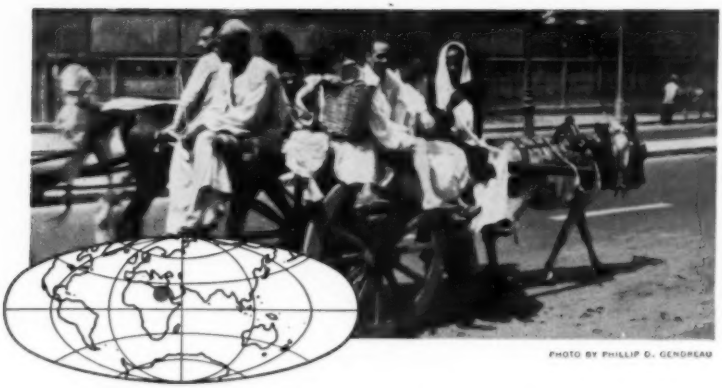

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This volume as the title indicates contains the papers and their pertinent discussions that were presented at the fourth international conference held in Geneva the latter part of 1957. The three previous conferences held in New York in 1948, Copenhagen in 1951 and Rome in 1954 evoked such interest in printed form that the officers of the International Poliomyelitis Congress decided to continue the practice of publishing the proceedings.

As could be expected there was proper emphasis on the problems of immunization with both vaccines, i.e. the one produced with inactivated viruses and the others with modified active viruses, the latter by Drs. Koprowski and Sabin. Several papers were devoted to the enteric viruses that produce disease simulating poliomyelitis.

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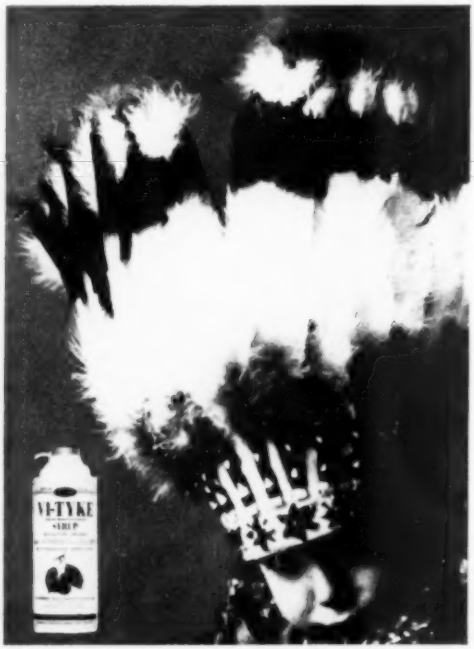

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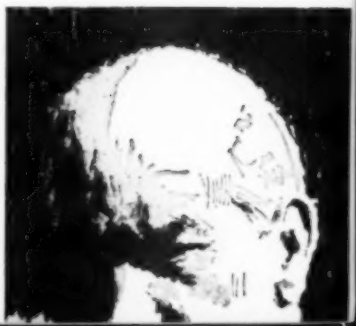

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guest editorials

The Pediatrician's Role in the Emergency Treatment of Eye Injuries

JOSHUA ZUCKERMAN, B.Sc., M.D., C.M., F.A.C.S.*

The pediatrician is often the first to be consulted in many cases of injury of the eye or eyes of an infant or child. Inasmuch as the initial treatment and management of such injuries may determine whether good or useful vision or whether blindness may result, the pediatrician should be familiar with the emergency care of this intricate, delicate, yet invaluable organ, called the eye.

A detailed history of the possible cause as well as of the circumstances under which the accident occurred is often extremely informative.

An injury to the eyebrow, margin of the orbit or eyelids is usually self-evident but its possible association with injury of the deeper parts should not be overlooked. Because contusions may have serious consequences, cases of this kind should be referred to an ophthalmologist. The pediatrician should not allow a child's "black eye" to become "a black eye" against him for having overlooked a ruptured sclera, a torn iris, a dislocated lens, an intra-ocular hemorrhage, a ruptured choroid, a hole at the macula, a retinal detachment, etc.

The most common emergency injury is that which results from a flying particle, namely, a foreign body. When lodged on the surface of the cornea (in the epithelium) it may be removed readily by a sterile moistened cotton tipped applicator. Preliminary instillation of a drop of a local anesthetic solution may facilitate removal.

When the particle is more deeply situated the use of an instrument is required and permanent scarring generally results. This type of case should be referred to the ophthalmologist who may

* Director Ophthalmology and Ophthalmic Surgeon Midtown Hospital, New York; Honorary Ass't Surgeon, N. Y. Eye and Ear Infirmary; Attending Surgeon Ophthalmological Foundation.

have to remove not only the foreign body but also a rust ring which often develops around a metallic particle.

It should be pointed out that from an optical point of view the most important area of the cornea is the central 4 mm.. Scars resulting from the inept removal of foreign particles in this area will interfere with vision. For this reason, cases of injury to this area should be handled with extreme caution and preferably referred to an ophthalmologist.

If the foreign body has already been imbedded in the eye for 24 hours, discomfort may be relieved by the instillation of a solution of homatropine (1 or 2 per cent). The continuous use of a local anesthetic for the relief of pain should be discouraged because it tends to dry, and to interfere with the nutrition of, the cornea. Comfort may be obtained by patching the eye and administering analgesics by mouth until an ophthalmologist becomes available, to remove the particle.

The eye should be examined on the following day to determine that tearing and redness have subsided, that healing is taking place and that signs of infection are absent.

A foreign body sensation may be simulated by many other conditions, for example, by a non-traumatic superficial lesion of the cornea. As the lesion progresses, the pain may even become more severe and widespread, and may be accompanied by blepharospasm, tearing and photophobia.

Recurrent erosion of the cornea may also follow a previous foreign body or other type of injury. It generally gives rise to acute pain during the night or on awakening in the morning.

Actinic keratitis is another cause of foreign body sensation and may be accompanied by pain, photophobia, tearing and blepharospasm. The history may reveal exposure to ultraviolet radiation from 1 to 10 hours previously. The conjunctiva is much less sensitive to pain so that foreign bodies of the conjunctiva may go unnoticed.

Foreign bodies may penetrate the anterior chamber and even injure the lens resulting in traumatic cataract. In many cases, gross clinical evidence of injury to the eye may be absent, or it may be detectable only after careful examination with special instruments. In the absence of a corneal or a scleral perforation, the presence of

softness of the eyeball, blood in the anterior chamber, a distorted pupil or a perforated iris may indicate that a perforation has occurred. X-ray of the eyeball and orbit are mandatory. Tetanus antitoxin may be required.

Lacerations of the cornea that have not penetrated the anterior chamber should be thoroughly cleansed, foreign particles removed, and the eye treated with antiseptic or antibiotic ointment and the application of a patch. If after a day or two the cornea in the area of the laceration becomes hazy, infection must be suspected and prompt local and systemic antibiotic therapy should be instituted.

Thermal and radiation burns may also cause discomfort or pain. Relief may be obtained by instillation of a local anesthetic, introduction of a soothing ointment, and by the application of a patch.

It is important to realize that alkali or acid burns usually cause permanent damage. Immediate, profuse and continuous irrigations of the eye should be made for at least a half an hour with saline solution or even with ordinary tap water. These cases should be referred to an ophthalmologist as soon as possible.

The alert, well informed pediatrician is fully aware that only by immediate, competent, meticulous attention to every eye injury can useful vision be retained and/or blindness be prevented. He seldom places the ophthalmologist in the unhappy position of being consulted only after the damage has been done, that is, after an injury has been misdiagnosed or mistreated so that complications have set in and vision is reduced or irretrievably lost.

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Osteogenesis Imperfecta

Review of Literature with a Report on Three Cases

S. Awwaad, M.D. Ch.* and M. Reda, D. Ch.*
Egypt

OSTEOGENESIS Imperfecta is a disease which occurs chiefly during infancy and childhood. It results from a defective mesenchyme. The disorder is congenital in origin, but, however, the time of appearance of clinical symptoms varies with intensity of involvement. Certain derivatives of the mesenchyme, usually the bones, the sclerae and the ligaments, are commonly involved, while others frequently escape.

The condition is known by many synonyms. The designation "Osteogenesis Imperfecta" was introduced by Vorlik[1]. Lobstein[2] used 'Osteopsathyrosis Idiopathica" in describing the occurrence of repeated fractures in infancy. There has been a tendency to use Vorlik's disease for the fetalis type and Lobstein's disease for the condition which develops in early childhood. Brailsford[3], however, commented that as all these terms refer to various examples of one and the same dystrophy, they should better be discarded for the all embracing term of "Osteogenesis Imperfecta". Other names less frequently used include Osteopsathyrosis Congenita, Malacia Myeoplastica, Osteitis parenchymatosa, Fetal Rickets and Annular Rickets.

The etiology is unknown. According to Fairbank[4], hereditary and familial influences play a part in the majority of cases and the disease can be transmitted through either parent. In some instances, the disorder has been followed through 7 generations. In one and the same family, however, the affection may vary from one member to the other e.g. one case may have blue sclerae, while another may suffer from otosclerosis or from multiple fractures. According to Rickel *et al*[5], blue sclerotics are commonly tied with hereditary but not with non-hereditary types, and according to Rodger[6], 60% of blue sclerotics tend to develop otosclerosis.

No hormonal disturbance has been cited as a causal factor and although there is diminished bone calcification, yet, the blood calcium, phosphorous and phosphatase are usually normal[7]. Mineral

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balance studies, however, reveal inadequate retention of calcium and phosphorous[8-10] and this is reasonable with such marked osteoporosis. Other blood chemical studies are found to be normal.[10-12]

PATHOLOGY

Bauer[13] was the first to describe a deficiency in the number of osteoblasts and irregularity of their pattern. There is diminished capacity of the mesoderm to produce the highly specialized osteoblasts, and instead, it produces cartilage like cells. There is absence of typical lamellar bone formation. Follis,[14] found that the reticulum spindles are not properly converted into collagen fibres i.e. there is failure of the reticulum to differentiate into mature collagen. Consequently, there is marked thinness of the cortex, relative scarcity of the matrix and paucity of islands of osseous tissue. The individual trabeculae are delicate and fragile. The periosteum is thin and irregular.

As a result of these changes, the bones in osteogenesis imperfecta are soft and can easily be cut through by a scalpel. Pliability, brittleness and deformities are characteristic features of the condition. In individual bones, however, there is great variation, from thin shafts with graceful curvatures to marked deformities with fractures and callus formation. There may be extreme angulation, sometimes very acute, even with reversal of direction of bone axis. In severe cases pseudojoints may be formed. The fractures vary from sharp breaks, to greenstick, to small fissures in the cortex. Healing may be by excessive callus or by a small one and is rapid but with defective bone so that fractures may recur in the same site.

Blueness of the sclera is due to its being much thinned. It is said to be one third the usual thickness, thus allowing the underlying choroid to become visible. Deafness is the result of otosclerosis, but is usually not met with in children, being a late manifestation that usually occurs by the end of the second decade or after.

In some cases there is laxity of ligaments and tendons and weak flabby hypotonic muscles, while in others, the skin may be thinned and of a fine texture (cutis laxa) or the teeth may show severe dysfunction of the odontoblasts and pulp tissue[15], together with deficient calcification of the enamel.

CLINICAL MANIFESTATIONS

Clinically the condition is classified into 4 types[16] which are:—

1. *Osteogenesis Congenitalis or Fetalis:* This is the most severe

form of the disease. Usually the infant is born dead or dies shortly after birth. However, three cases that lived up to 19, 29 and 68 years of age, are recorded in the literature.[4, 17] Fractures commonly occur in utero and are frequently encountered during the act of delivery so that the infant is born already deformed. The bones are so soft that even very gentle handling of the baby may produce fractures and as many as 100 fractures have been recorded in a newborn. Palpation of the skull conveys a sensation likened to grasping a bag of water. The thoracic cage is frequently misshaped.

Radiologically: The long bones of the extremities appear much thickened and stunted as in achondroplasia, but they are osteoporotic and show multiple fractures with ample callus formation. Because of these radiological findings, Fairbank[4] titled this group "The Prenatal Thick Bone Type".

2. *The Infantilis type:* This is a less severe form in which the infant is born apparently normal or with only blue sclerae. Then it appears to progress satisfactorily until the first fracture which is likely to result from a fall in learning to stand or in taking a few steps. The intensity of involvement varies greatly. Some children may suffer only an occasional fracture, while others suffer fractures so frequently and easily that they must have continuous confinement. A small number have only an occasional fracture and are able to attend school. According to Brailsford[3] the plasticity of bones appears to consolidate in early adult life (after puberty) so that little or no progress in the condition occurs after that.

Radiologically: The skeleton as a whole is markedly osteoporotic. The long bone of the extremities are slender, and being soft, they show varying degrees of deformaties and fractures. Hence, Fairbank describes these cases as "The Slender Fragile Bone Type". The cortex is practically absent, while the epiphyseal ends are large and usually have a honeycombed appearance. Transverse lines of dense bone are often seen at the end of the metaphysis. The cervical spine may invaginate the base and cause the latter to sag posteriorly resulting in false shortness of the neck. The vertebral column and the pelvis are usually osteoporotic and that is why kyphoscoliosis and triradiate pelvis are common. The ribs as well frequently bow and fracture, causing varying degrees of deformity of the thoracic cage.

3. *The Tarda Type:* This is still a less severe form. It includes cases having a more substantial ossification of the skeleton at birth. Consequently the fractures or deformities usually occur during late childhood i.e. by the end of their 5th year or later. In this type the outlook as regards life is usually good, although the deformities frequently interfere greatly with their activities and they usually end up as miserably deformed dwarfs.

4. *The Adulta Type:* This is an exceedingly rare type in which the patient after an apparent arrest of the infantile or tarda types, develops recurrence of skeletal fragilty again in adult life.

TREATMENT

There is no specific treatment. In the congenital type, the baby should be kept on a bed of cotton wool and should only be lifted for changing. The procedure of diaper changing requires exquisite technic in manipulation. At all ages, however, great care must be taken to set the fractures in as perfect alignment as possible, in order to reduce the liklihood of further deformity.

CASE REPORTS

Case No. 1 (fig. 1) M.M., a female, was 50 days old when first admitted to Abbassia Childrens' Hospital on 2/1/57. She is a typical example of Osteogenesis Imperfecta Congenitalis. The mother gave the history that the baby was born with severe deformities in both upper and lower limbs together with a markedly soft skull.

Family History: Parents are relatives. They are middle aged and both are normal and in good health. They have been married for 15 years, during which period the mother aborted once and gave birth to 6 full term normal infants. The first 3 died and according to the history given by the mother, two of them died during their first 2 weeks of life, from some unknown cause, while the third died at 6 months of age with a history exactly similar to that given by the present case. Of the three living children, the first is 5, and the second is 2½ years of age and both are enjoying normal health, while the 3rd is the present case.

Prenatal and natal history: The mother had a normal pregnancy and delivery but the infant was born with severe deformities of both upper and lower limbs.

On Examination: The infant (fig. 1) was evidently below normal

Fig. 1. A case of Osteogenesis Imperfecta Congenitalis. Notice: 1—Prominence of Eyes. 2—Deformity of Limbs. 3—Wrinkling of the skin.

weight and length (being 2.9 Kg. Wt. and 18 inches long). The bones of the skull showed marked defective ossification, and craniotabies was easily elicited. The eyes were prominent with blue sclerotics. The skin covering the trunk and limbs was very lax, thin and wrinkled. The upper and lower limbs showed marked deformities with much irregularity of their bones but the chest and spine were apparently normal.
Clinical examination of the heart, lungs and abdomen showed no abnormality.

Laboratory Investigations: Hb. 75%, R.B.Cs. 4,200,000 W.B.Cs. 15,000 with 65% lymphs, 35% polys. 3% mono, 1% Eosin. 1% basophils. Blood calcium 11.5 mg%, phosphorous 5.3 mg% and alkaline phosphatase 25 K.A. units; W.R. was negative for both the infant and mother. The average S.R. was 5 (Westergren). Urine and stools were normal.

The X-ray findings were as follows: (1) The skull shows partial ossification in some parts of the occipital, parietal and frontal bones. (2) The bones of the chest show irregular broadening of the ribs at sites of fractures and callus formation. However, the general configuration of the chest was normal. (3) The long bones of the limbs (fig. 2. a & b) are broadened, reaching 5-6 times the normal. They show generalised decalcification and have a crumpled up ap-

pearance due to numerous bone fractures with ample callus formation.

Follow Up: The patient remained in hospital for 4 weeks, and was discharged at request of her mother. She died 3 months later of an intercurrent bronchopneumonia after sustaining some more fractures in the bones of the limbs and ribs. In an X-ray, taken of her 2 weeks before death, the limbs still showed the features of "The Thick Bone Type".

The Second and Third Cases: were two sisters and are respectively examples of the Infantile and Tarda types. They were both ad-

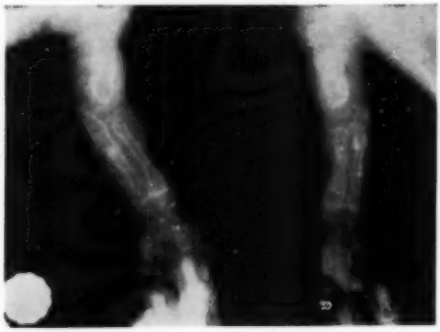

Fig. 2. Xray of long bones of upper limbs of Case No. 1 showing features of the "Thick Bone Type". Notice: 1—The marked broadening of the long bones. 2—The generalized decalcification. 3—The crumpled up appearance due to numerous bone fractures with ample callus formations.

mitted for the first time to Abbassia Childrens' Hospital on 22/2/55, and since then they were followed up in both the in and out patient departments.

Family History: The parents are relatives and are middle aged. Both looked normal and healthy. The mother aborted 6 times and gave birth to 7 full term, apparently normal infants, of which 4 died and 3 are still living. According to the mother, a picture of osteogenesis imperfecta developed in one out of the 4 cases that died. Out of the 3 living children, two suffered from this disease and they constitute the 2nd and 3rd cases in this report. No history suggestive of the presence of the condition in other members of the family could be elicited.

Gestation and Birth history: In all the 3 cases which showed the disease, the mother had normal pregnancy and labour and the babies at birth were all apparently free from deformities.

Case No. 2: (fig. 4) A.A., a female, was the 4th birth in the family, she was about 12 years when first admitted with the complaint of (1) inability to walk that dated since birth, (2) severe deformities of the limbs and trunk. (3) marked tendency to develop fractures on minor traumas.

Past History: The patient appeared normal at delivery and showed normal development during her first year of life. She was able to sit at six months of age and creep at 8 months. However, she was unable to stand up in the usual time, for which reason she was given repeated courses of ultra-violet therapy but irrespective of that her inability to stand continued until her 4th year of age, when she became able to stand and walk when supported. Soon after, however, she sustained her first fracture in her Rt. femur as a result of an insignificant trauma. Since then, she suffered from numerous fractures in her left upper and both lower limbs. The early fractures used to occur in periods of 3 to 6 months but the late ones occurred after longer periods.

Fig. 3. Xray of long bones of lower limbs of Case No. 1 showing the features of "The Thick Bone Type" mentioned in (fig. 2).

On Examination: The patient was a crippled dwarf (fig. 4), markedly under weight and height, (being 17 Kg. Wt. and 105 cm height). She looked anemic and was sitting in bed talking, when interviewed, solemnly and intelligably and she appeared to know much about her illness. The skull was of normal circumference, with well united sutures and closed fontanels. The eyes, sclerae, teeth and skin were all normal. The chest was severely deformed. Anteriorly it showed a marked forward bulging in the middle third

Fig. 5. Xray of skull of Case No. 2 Notice: 1—The platy-basia. 2—The prominence of the jaws.

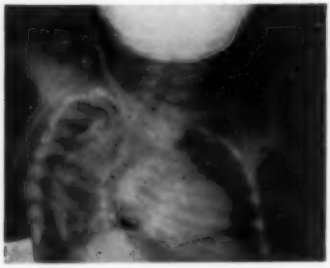

Fig. 4. Photo of Case No. 2 Notice: 1. The marked wasting and stunting; 2. The deformity of the chest; 3. The deformity of left thigh; 4. The apparent shortening of the neck.

Fig. 6. Xray of chest of Case No. 2. Notice the marked deformity of the chest.

of its lower half, while posteriorly it showed also another bulging occupying the whole right side, with an overhanging of the corresponding scapula. The spine showed a severe kyphoscoliosis of the dorsal and upper lumbar vertebrae. The limbs were remarkably slender and their muscles showed marked wasting. The right upper limb was free from deformities while the left one showed a severe angular deformity at the middle of the forearm. The lower limbs, on the other hand, showed severe ankylosis of both hip joints; apparently the femoral heads were locked and permanently fixed into their acetabular fossae and this resulted in marked limitation of movements at these joints. The left femoral bone showed a marked antero-lateral bowing (fig. No. 5).

Clinical examination of the heart, lungs and abdomen showed normal findings.

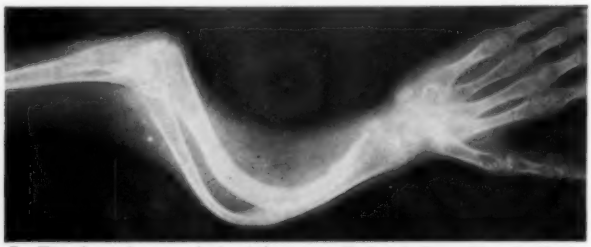

Fig. 7. The long bones of the left upper limb of Case No. 2. Notice the angular deformity of the bones of left forearm.

Investigations: Hb. 60%, R.B.Cs. 3,200,000, W.B.C. 6.000 with 66% polys. 32% lymph. 2% mono. and 0% basophils and eosinophils. Average S.R. was 4, W.R. negative. Blood calcium 11 mg.%, phosphorous 3.5 mg.% and phosphatase 22 K.A. units. Urine and stools were normal.

X-ray films revealed the following: (1) The skull (fig. 5) showed (I) "Platybasia" resulting from upward invagination of the skull base by the upper cervical vertebrae with consequent sagging of the occipital fossa (II) marked prominence of the jaws. (2) The bony thorax (fig. 6) showed (I) severe kyphoscoliosis of the dorsal spine (II) severe rarefaction of the vertebral bodies with multiple wedge shaped deformities (III) generalised disfigurement of the bony thorax; the intercostal spaces in some areas were markedly narrowed and in others showed widening. (IV) the ribs were the seat of generalized rarefaction and multiple fractures with evidence of healing and union of adjacent ribs at sites of their fractured parts. (3) The bony pelvis showed: (I) generalized severe osseous rarefaction (II) advanced irregular contraction and narrowing of the pelvic cavity (III) marked invagination of the left ischium and acetabular fossa by the head of the femur. (4) The long bones of upper and lower limbs showed (I) severe osseous decalcification (II) severe bending of the long bones of left upper limb and of both lower limbs with multiple pathological fractures and evidence of healing (III) generalized narrowing of all the joint spaces with thinning of the articular surfaces. (Fig. 7).

Follow Up: The patient is now followed up for almost 4 years. Apparently the fractures are becoming much less frequent; as durthe last two years she had sustained one fracture only in her left femur. However, she is still a crippled dwarf and her puberty is arrested as she is now over 16 years of age and yet her menstrual cycles have not started and the pubic and axillary hair have not grown.

Fig. 8. Photo of Case No. 3—lateral view. Notice: 1—The deformity of the chest. 2—The deformity of the spine.

Fig. 9. Xray of chest and spine of Case No. 3. Notice: 1—The disfigurement of the chest. 2—The severe deformity of the spine.

Case No. 3: (Fig. 8) This case is the younger sister to the above mentioned case and is an example of the tarda type. She is the 9th birth in the family. She was 6 years of age, 4 years ago when she was first admitted to hospital with her elder sister. On admission she complained of severe deformity of the chest which was of one year duration but no history of fractures was given. During her development she was able to sit, walk and stand in the usual time. On examination the patient looked anemic, stunted and markedly under weight (11 kg. Wt and 88 cm height). However, she showed a normal mental development. The skull was of normal size and shape but on the other hand the chest was severly deformed showing a marked anterior bulging and a severe posterior kyphoscoliosis. The upper and lower limbs appeared normal. Clinically the heart, lungs and abdomen were normal.

Laboratory investigations showed no peculiarities as in the above mentioned two cases.

X-ray films of the bony skeleton revealed that the affection was mainly limited to the bony thorax and the spine, while other bones

appeared more or less normal. The following were the main points noticed:

1. The bones of the skull appeared normal and there is absence of "platybasia".
2. The thoracic bones (fig. 9) on the other hand showed generalized and marked rarefaction of the ribs and the vertebral bodies with severe deformity of the chest cage but no evidence of old or recent fractures at all.
3. The vertebral column (fig. 9) showed marked kyphoscoliosis in the dorsal and upper lumbar regions.
4. The long bones of the limbs showed a normal picture except for several horizontal lines of arrested growth at the lower ends of both tibias.

Follow Up: During the succeeding 4 years the patient sustained no fractures. She is now attending her school regularly and is apparently getting on normally.

SUMMARY

A review of the literature on Osteogenesis Imperfecta is given together with a report on 3 cases. The first case is a typical example of the congenital type, while the second and the third cases are sisters and are respectively examples of the Infantile and Tarda types.

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Gamma Globulin in Preventing Infections in Premature Infants

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INFECTION is a well-known cause of morbidity and mortality in premature infants in the first month of life. In the Pediatric Department of Ullevaal Hospital, a great frequency of infections occurred among premature infants before a separate ward for prematures was opened in November 1958. Up to this time, most infants in the smaller weight groups, both non-infected and infected, were nursed by the same personnel. In these circumstances, nosocomial infection was difficult to prevent. A staphylococcal epidemic in all the municipal obstetrical departments appeared in 1957-1958 with a frequency of mastitides up to 25% as well as pyodermias among the newborn infants with an even higher percentage[6]. In the same period many prematures in the children's department had mild or severe infections dominately caused by staphylococcus aureus[7].

The transient hypogammaglobulinaemia of early infancy is a physiological phenomenon which under normal circumstances is of no clinical significance[4]. In premature infants this low level of serum gamma globulin is more marked.[2,3,5] Antibodies are known to be of a gamma globulin character and many reports are available about the relation between congenital or acquired hypogammaglobulinaemia and frequent infections. There is no established critical level of serum gamma globulin below which lowered resistance to infections occurs[5].

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Treating premature infants with gamma globulin in preventing infections are mentioned by Janeway & Gitlin[1] and Pearce[5], but so far no investigation seems to be published about this.

The object of the present paper is to evaluate the effect of gamma globulin given to premature infants in preventing infections the first months of life.

MATERIAL

This report includes 20 premature infants with birth weight ranging between 1000 and 2000 grams. Ten of the infants were given injections of gamma globulin about every half month from the age of two weeks. The preparation of "Kabi" was used containing 16% gamma globulin. The dose was 0.5 cc. per kilogram body weight. We had planned to continue this treatment up to the age of 4 months, but this was done only in five cases. Among the other five—two infants were treated within the first 3 months—one within 2½ months, and the two remaining infants within 2 months. The range of total gamma globulin given was from 3 cc. to 10 cc. The other ten premature infants served as a control group. The average birth weight was the same in both groups (1630 g.). The first group consisted of four males and six females—in the control group were three males and seven females. The observations were continued after discharge from the hospital up to the age of one year—except for two infants in both groups who were followed for only 3 months. Venous blood samples were taken about every two weeks for determination of gamma globulin levels in serum. These tests were examined at the Central-laboratorium, Ullevaal Hospital by paper-electro-phoresis. A total number of 111 blood samples were tested.

RESULTS

In the group treated with gamma globulin, two infants, both at the age of 6 weeks were seriously ill with pneumonia—but recovered. Both had gamma globulin levels in the lower range when they became sick (0.38g. and 0.49g. percent). Further, two infants of this group had pneumonia, at 5 weeks and 8 months respectively, but neither was seriously affected. One infant developed septicaemia within two days after the first gamma globulin injection but was probably sick before treatment started: she recovered from the infection. Among the remaining five infants two had pyodermia at the age of one and three months respectively.

In the control group two infants were seriously ill of pneumonia —one at the age of six weeks—the other at 3 weeks as well as at 10 weeks of age. Both had gamma globulin values in the upper range at the time of illness (0.70g., 1.11g. and 0.53g. percent). Another infant also had pneumonia, but recovered with a few days. Two infants had pyodermias at the age of 2 and 5 weeks respectively. One infant had otitis media at the age of 5 months.

Thus in both groups two infants had a severe infection; mild infection occurred also with the same frequency (four in both). Three of the infants treated with gamma globulin developed varicellae before the age of one year.

The determinations of gamma globulin in serum from the infants in both groups are given in Table I. The pronounced decrease in the gamma globulin values from about 1 g. percent at birth to about 0.5g. percent at the age of one month is well known. The following three months the infants who received gamma globulin showed some higher values compared to the control group. The infants in the gamma globulin group had rather lower values from six to twelve months old. It is evident that great differences were recorded in gamma globulin values within the same age groups. As mentioned by Janeway & Gitlin, paper electro phoresis is a less exact method for determination of gamma globulin in low concentrations.

Table 1. Gammaglobulin in Gm. per 100 cc. blood from infants at different ages given gammaglobuline-injections and from a control group.

	"GAMMAGLOBULIN" GROUP			CONTROL GROUP		
Age:	*No. of tests*	*Mean*	*Range*	*No. of tests*	*Mean*	*Range*
At birth	2	1.30	0.77 - 1.83	2	1.13	1.05 - 1.21
½ month	5	0.96	0.61 - 1.43	6	0.89	0.70 - 1.11
1 month	7	0.59	0.33 - 1.07	7	0.58	0.18 - 1.04
1½ months	8	0.57	0.38 - 0.82	6	0.54	0.38 - 0.70
2 months	4	0.54	0.36 - 0.70	7	0.51	0.24 - 0.61
2½ months	2	0.65	0.52 - 0.77	8	0.56	0.47 - 0.70
3 months	4	0.67	0.55 - 0.94	6	0.36	0.22 - 0.58
3½ months	3	0.43	0.35 - 0.48	3	0.42	0.35 - 0.51
4 months	5	0.63	0.36 - 0.73	4	0.52	0.41 - 0.73
6 - 8 months	6	0.58	0.23 - 0.77	5	0.61	0.30 - 0.89
12 months	8	0.74	0.55 - 0.92	3	0.78	0.39 - 1.54

DISCUSSION

The high frequency of infections among the premature infants in 1958 in the Pediatric Department of Ulleval Hospital was the reason for this study. Ten infants in the group treated are of course too small a number for significant conclusions. Greater doses of gamma globulin might prove more effective particularly if given

from birth. The infections described were predominately caused by staphylococcus aureaus; gamma globulin in other types of infection might prove effective.

SUMMARY

Two groups of premature infants, ten in each, are compared on the basis of infections occuring in the first year of life. One group had semi-monthly injections of gamma globulin and a total doses of 3 cc. to 10 cc. were given. Severe and mild infections (staphylococcic) occured in both groups with the same frequency. III venous blood samples were examined for gamma globulin by paper electrophoresis. Some higher values were found in the gamma globulin group. Severe infections were not correlated with an extremely low gamma globulin values in serum.

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Biochemical Influences in the Etiology of the Unusual Child

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Although it is well recognized that a portion of the abnormalities of children are due to birth injuries or result from genetic sequence, there exists among the "unusual children" a large percentage who apparently show no evidence of natal injury and whose hereditary history fails to reveal any pattern which can explain their deviations.

The recent broadening of biochemical knowledge to the borders of the sciences of cytology and axial physiological gradients provides evidence that the clues to the etiology of the abnormal child or mutant may lie in a better understanding of the biochemistry of both the parent and the child involved.

In approaching the problem of the biochemistry of the abnormal child and its parent there are important biological axioms that should be recalled:

1. The key to every biological problem must be finally sought in the cell.
2. Protoplasm owes its nature to its chemical organization rather than possession of some one vital element.
3. The prime instinctive function of the chemical organization of the cell is the oxidative-reductive process.
4. The chemical organization of the cell quickly disentegrates without an immediate reservoir of oxygen.
5. The property of self-preservation is a primary instinct of all living things and is a peculiarity of the oxidative-reductive process.

This biochemical hypothesis has been accepted for publication because it presents a somewhat unorthodox but interesting approach to some of the unsolved problems of infancy and childhood. It is believed that this concept will prove stimulating to readers.

6. The cell characteristics of irritability and adaptability are manifestations of cell organization. Under varying ecological influences, these properties affect the cell to make physical and constitutional adjustments in its structure in order to accommodate itself to its new environment. Many of these responses are not desirable in complex cell organization, but they are the best response the cell can make to the introduction of extrinsic environmental factors into its media.

7. The cell membrane is of vital importance in cell function because: (a) it is the initial sensory medium which affects the adaptation of the cell, (b) it enjoys the specialized osmotic quality of selective permeability. Variations in its permeability, through the introduction into intercellular areas of elements which affect the osmotic qualities of the cell membrane, can produce extreme changes in normal cell structure.

8. The cell is a highly organized system of oxidative enzymes together with their substrates and electro-chemical materials, such as chromatin. It is a truly reversible system with a potential affected by the ratio of the "oxidized" to the "reduced" from the substrate.

9. No absolute equilibrium exists but, rather, a steady state resulting from an incessant and simultaneous oxidative and reductive process in both directions, i.e. in and out of the cell.

10. Any change in this steady state of oxygen tension will profoundly affect the activity and the structure of the cell.

In axial physiological gradient studies of the sea urchin, demonstrating the organization of the cell and involving its metabolism and conditions associated with or resulting from its metabolism, exposure to any of a large number of toxic external agents resulted in graded differential inhibitions to its development. The regions normally graded at the highest levels were most retarded.

In teratological studies of man and other vertebrates, it was noted that, although *apparently* heredity is the primary factor, it was necessary that environmental factors producing varying degrees of inhibition in the early development of the organism were a prerequisite to the formation of abnormal offspring. Otocephaly, cyclopia, and related defects have been produced in fish and in amphibious embryos by chemical inhibitors to which the head is especially sensitive.

A remarkable feature of teratological development is the association of multiple abnormalities in complex syndromes. Thus, in man, hairlip, spina bifida, hydrocephalus, and polydactyl may be found in the same individual. In acrocephalosyndactyl, we find an egg-shaped skull, fission of the digits in both hands and feet, in addition to hair lip, contractures, spina bifida, and mental abnormalities. *Although some defects can be attributed to a single defective gene, the biochemist hypothesizes that these abnormalities are produced by various toxins, cell respiratory inhibitors, or mechanical interference with the osmotic function of the cell membrane.*

POST-NATAL BIOCHEMICAL INFLUENCES

In applying the above annotated biological studies to the understanding of the abnormalities of the child, the more rational approach to an understanding of the biochemistry involved is to study and make observations of the unusual child who, apparently, has had no birth injury, reveals no genetic defects, and yet, either fails to develop normally or suddenly stops developing in the first years of its life.

To fully understand what may occur in the body chemistry to produce the inhibitory factors that cause retardation, an understanding of the lipoprotein complex and its varied densities, as expressed by the Svedborg flotation units, is necessary.

It is the presence of cholesterol in the lipoprotein complex which gives it a lower density than that of ordinary protein. Cholesterol is the principal sterol of the higher animals and is found abundantly in all the tissues and, especially, in the brain and spinal cord. It exists in the plasma in two forms, free and as esters incorporated into lipoprotein molecules. It is found in adipose tissue as part of the fat complex, but, whereas the fats are saponifiable, neutral, glycerol esters of oleic, palmitic and stearic acid, cholesterol is a non-saponifiable sterol which appears free or as an ester. It is the property of easy ester formation that lends to cholesterol the important property of transport of protein products to the cell, and the removal of non-protein nitrogen wastes from the cell. *It is the involved relationship of cholesterol to the non-protein nitrogens, the extreme changes in the physicochemical nature of the compounds formed that appear to be important in understanding the retardation that may occur in the development of the child.*

The non-protein nitrogens of the blood include urea, uric acid, amino acids, creatine, creatinine, ammonia, and a fraction designated as "undetermined nitrogen". All of these non-protein nitrogens, with the exception of uric acid, are highly diffusible and easily handled by the body.

Uric acid, the chief end product, in man, of purine metabolism, is only slightly soluble in body fluids. Being an acid, it is the only one of the non-protein nitrogens that suggest a biochemical parallel to lipoprotein formation. Because of the slight solubility of uric acid, and because man lacks the enzyme, uricase, to convert uric acid into allantoin, and because of man's limited efficiency in clearing uric acid from the plasma through the glomerular filtrate, there are times when high purine ingestion, faulty kidney function, or disturbed uric acid metabolism result in an accumulation of uric acid.

This storage of uric acid first takes place in the blood, but, owing to the characteristic of the low solubility of uric acid and its salts, only a limited quantity can be controlled by the buffering quality of the plasma. Other excess uric acid may remain, within the limits of its solubility, in the intercellular fluid or in the fluid protoplasm, or it may crystallize in various parts of the body as acid sodium urate, or form, with cholesterol, a wax compound of unusual physicochemical properties.

In the laboratory, cholesterol urate was formed at concentrations of cholesterol and uric acid in the proportion of about 24 mg. cholesterol and about 6 mg. uric acid per 100 cc. It did not appear in lower concentrations and it required from ten to fourteen days for the cholesterol urate to appear.

The cholesterol urate "in vitro" took the form of platelets or clumps, was membraneous in nature, and strongly hydrophylic. The normal, negative flotation properties of cholesterol compounds assumed a positive sedimentation with increased specific gravity. In addition, the electrochemical property of strong attachment to surfaces manifested itself.

The relationship of these observations to the biochemical influences in the development of the child is indicated by the history of the studies of protein metabolism and the problems of uric acid disposal. Both of these bodily functions have long been associated with the pathologies of early childhood. Children's diseases, such

as, rheumatic fever and the hyperkinetic and neuropathological patterns of chorea have been shown to bear a constant relationship to uric acid metabolism.

During the first days of life, the infant gives evidence that, in its prenatal development, it has accumulated large quantities of uric acid; for the urine of the newborn child contains 7 to 8% of the total nitrogen in the form of uric acid as compared to 1 to 2% in the adult. This may lead to the development of urate infarcts in the kidney of infants because of the extreme insolubility of uric acid in acid media. If this condition persists and interferes with normal kidney function, it is capable of producing a toxicity which, in its turn, effects a general retardation of the child in its development.

Although the pathologies of faulty uric acid handling have always been related to patients of advanced age, attention should be called to the fact that cases of initial attacks of gout have been reported as occurring as early as the first decade of life. It should also be noted that the earlier in life the first attack developed, the stronger the disease and the greater the incapacity.

It is likely that, in the normal child, the large quantity of uric acid that appears at birth is controlled by proteolytic plasma factors. These enzymes, originating in the pancreas, have the property of preventing an association of uric acid with cholesterol or of digesting cholesterol urate already formed. These plasma constituents of the trypsin group are capable of controlling many of the obscure inflammatory pathologies of all age groups by eliminating the congestive cause of the inflammation. Laboratory work done by the authors of this paper showed that the phospholipoids are an important plasma constituent in the control of cholesterol urate. Choline easily digested cholesterol urate "in vitro".

It should be noted that, normally, the decline in the high percentage of uric acid in the blood plasma of the child is rapid and, therefore, the direct quantitative relationship of the proteolytic enzymes to uric acid is not distorted for too protracted a period.

If this rapid decline in uric acid does not take place and, for various reasons, the plasma uric acid is maintained at high levels, the proteolytic enzymes cannot retain their quantitative advantage of keeping the compounds of cholesterol and uric acid disassociated. There is every likelihood that cholesterol urate will form, bringing with it sclerosis, congestion, inflammation, and attendant problems.

The physicochemical qualities of cholesterol urate's high specific gravity and water retention, together with the electrochemical qualities of strong surface attachment, interfere with the normal ability of the circulatory system to supply affected areas with an adequate supply of oxygen. By clinging to cell surfaces, cholesterol urate also interferes mechanically with the normal oxidative-reductive processes of the cell membrane and, therefore, retards cell processes.

The pathologies of congestion may be further complicated by acute infection which is capable of elevating the normal 200 to 400 mg. per 100 cc. of fibrinogen to values up to 1,000 mg. per 100 cc. This occurs in the infections attendant upon septecemias, bacteremias, and pneumococcic pneumonia. Lesser elevation is observed in nephrosis, sinusitis, tonsillitis, and cholecystitis.

Although fibrinogen and fibrin are usually well controlled by plasmo fibrinolysin, it can be understood that, since biochemical relationships of this nature are purely quantitative, an elevation of fibrinogen and fibrin by infective pathologies can, in the presence of an actual or incipient cholesterol urate congestion, further increase the cell difficulties of adequate osmotic respiration. This would be quickly reflected in the rate of physical and mental development.

The failure of an adequate oxygen supply results in an inhibition or an inadequate stimulation to the growth of the cerebral cortex producing fine changes in the nervous system and in the brain. These modifications from usual development, which can occur either in childhood or foetal life, can produce the multitude of aberrations from normalcy, ranging from epilepsy, mental defects, cerebral palsy to general retardation in both physical and mental forms.

It should also be noted that, in many of these unusual children, the heart and blood vessels, which have the faculty of developing in direct relationship to respiratory demands, are abnormally small.

In those cases in which the apparently normal child suddenly slows in its development, it is, most likely, the respiratory, inhibitory, biochemical resultant of congestion and sclerosis by cholesterol urate and cholesterol urate-fibrinogen masses. This phenomenon can occur at any stage of the child's development. Whenever this occurs in the proximity of important centers of the nervous system or in the ocular or otic regions, the pressures generated

in the child may be manifested by developing the child into the nervous, the neurotic, the emotionally disturbed, or the schizophrenic. Since these biochemical effects occur haphazardly, it is impossible to give an index of degree or classification of the intensity of the effect upon the child or predict correctly the course these pressures may take. Typical symptoms of nerve and circulatory congestion may be noted in digital rigidity, spasticity, and rigidity of the neck muscles. The child, as an organism incapable of coping with the unfavorable biochemical environment becomes confused, undeveloped, and makes adaptations in retarded forms.

A purely physical and physiological effect upon the child by the biochemistry involved in uric acid and cholesterol urate is rheumatic fever which reveals seasonal patterns, social and hygiene factors, and familial tendencies based purely on a rheumatic history. Constant studies have failed to reveal a Mendelian mechanism. It is important to note the raised erythrematous lesions and subcutaneous nodules which are generally accepted as diagnostic of rheumatic fever and could readily be produced by deposits of cholesterol urate.

Histochemical studies of the lesions and subcutaneous nodules concurrent with rheumatic fever revealed a fibrinoid structure which further studies may show to be the cholesterol urate-fibrinogen or fibrin mass described above. That it is not a pure fibrin mass is attested by the fact that it resisted tryptic digestion. It is most likely this same material that produces the atherosclerosis of later life.

Idiopathic epilepsy is a symptom complex which points to an etiology of a biochemical character. Approximately sixty percent of the children who have recurrent convulsive disorders before fourteen years of age have idiopathic epilepsy. The onset is between the ages of four and eight years in 50% of the children, and less than 2% of them have a convulsion before the age of two. Although electroencephlographic tracings, particularly during sleep, show definite, generalized abnormalities in 90% of children with idiopathic seizures, their abnormalities are not focal, are migratory, may be incidental to the seizure, may be the result of the seizure, or merely record causative biochemical congestion.

Heller's disease is another of the obscure illnesses of childhood that give evidence of a biochemical change resulting in a pathology. Histological examination produces evidence of sclerotic, cortical

neurons, lipid deposits, and meningeal fibrosis. As in epilepsy, the onset does not occur in the neo-natal stage of the child, but in the third or fourth year of life. The illness is progressive, usually initiated by an infection. The child becomes irritable, disobedient, has tantrums, begins to regress in speech and in signs of mentation. Within a year, he is mute, pays no attention to speech, may have tics, is incontinent, and often has to be fed. In light of the histological evidence and the progressive nature of the biochemistry of sclerosis, the clue to Heller's disease, as in epilepsy, may be in an uncompensated failing in the metabolic mechanism of the child. Since man, at every stage of life, gives evidence that many of his pathologies are linked to his inability to handle excessive quantities of the non-protein nitrogens or some of the cholesterol esters of high specific gravity, it would be well to mark these compounds as, possibly, being responsible for the abnormalities of Heller's disease.

In the perspective of the material so far presented, there are areas in the pediatric care of the child that are subject to reexamination. The overemphasis of proteinization of the infant's diet in an apparent attempt to hasten its development, the indiscriminate use of multiple vitamin preparations as a "buckshot" method of insuring the child's health may not only delay the elimination of natal non-protein nitrogen, but actually add to its percentage in the plasma. By incorporating into the feeding habits of an infant high protein, purine-rich foods, by including such preparations as liver extract, by the use of vitamin formulas rich in B_{12}, B_1, and C, an excessive exogenic and endogenic production of the non-protein nitrogen is insured. This over-proteinization and over-vitaminization can produce a toxic cell environment which interferes, both chemically and mechanically, with cell respiration and results in a neurological reaction which manifests itself in a variety of symptom complexes.

Although the kidney, the skin, and the alimentary canal are important media for ridding the body of the non-protein nitrogens, very often, particularly when they appear in excess, the body attempts detoxication by oxidation. In its effort to rid the body of the slightly soluble uric acid, it resorts to oxidation; but, since the oxidized products of uric acid are parabanic acid, barbituric acid, and related products of great toxicity, the child is not relieved of

his problem. *The oxidative products of uric acid cause a toxemia, producing fatigue, depression, and hypnosis.*

One of the more important excretory sites of the non-protein nitrogens is the mucous lining of the entire length of the alimentary canal. It is in this area that some of the errors occur that complicate the biochemistry of the child. Uric acid, particularly, is converted by the bacteria of the lactobacillus group into compounds more easily disposed of by the body. This is one of the great advantages that accrue to the breast-fed baby because, in addition to human milk providing a lower alimentary PH favorable to the child, the bacterial content is predominantly of the lactobacillus group. This contrasts to the predominance of the coliform bacteria in cow's milk. In addition to these basic waste-handling advantages, it should be pointed out that cow's milk contains seven to eight times the amount of casein found in human milk. This is a basic protein which evolves, eventually, into nucleic acid and, ultimately, into endogenic uric acid. In addition, human milk is alkaline or amphoteric, while cow's milk is acid or amphoteric. This variation in PH may also be an important contributing factor in handling alimentary non-protein nitrogens.

PRE-NATAL INFLUENCES

The abnormal child in the neo-natal stage may be the product of a genetic sequence which is reflected in its family history, but may have deviated from normal development under the influence of maternal disease or biochemical change. Although, in the case of genetic defect, the abnormal child may receive its malformation by transmission from either parent, it is hardly likely that a structurally defective spermatazoa can fertilize an egg and, if this did occur on occasion, the fertilized egg, most likely, would be aborted during the period of gestation. Embryologists are agreed that defects in the human embryo, caused by direct injury or continued pressure, are hardly likely in the human embryo; the sheltered intro-uterine habitat of the foetus greatly reduces the likelihood of mechanical injuries playing a significant role in the causation of anomalies.

On the other hand, since the embryologists have shown that changes in the relative amounts of various chemicals in sea water can cause the production of several different types of deviation in fish embryos and, since they have shown that an insufficient quantity of oxygen can produce a wide variety of embryo forms, and since

they can also produce malformations of a particular type by withholding specific vitamin fractions, it is possible that the answer to human embryo aberration may be traced to a change in its biochemical environment.

The role that disease plays in creating a biochemical environment conducive to abnormalities is well recognized. The importance of German measles in the mother during the first three months of pregnancy as a cause of congenital cataracts, cardiac abnormalities, microphthalmos, and deaf mutism, has been established

The statistics of Mongolism demonstrate that, although mothers of any age, including the very young, may give birth to a Mongolian infant, the average maternal age for such births is almost ten years greater than for random ones.

In the many indeterminate abnormalities that occur during the prenatal life of the child, it is quite likely that biochemical changes initiated by hyperuricemia and complicated by the formation of cholesterol urate may produce the pressures, toxicity, and anoxia that retard or distort the embryo into the unusual child.

Although the human female has been thought to enjoy estrogenic barriers which shield her against the more extreme pathologies of non-protein nitrogen toxicity, the presence of gout in young female patients as young as 14 years and an approximate ratio of one female to each ten male cases give evidence that, in many women, the estrogenic, proteolytic or fibrolysin quotients are not adequate to protect them from the various pathologies of hyperuricemia.

Hyperuricemia in its manifestations beyond the rheumatoid and gout forms develops into non-determinate, pathological forms which are hyperkinetic and neuropathological. One of the essential causes of change in the environment of the neurones is an abnormal condition of the blood and lymph. This ecological change for the neurones can be produced by the excess of certain normal constituents of the blood, such as the nitrogenous wastes. If oxidation of this material is incomplete or these substances accumulate in the blood, uremia supervenes with symptoms of polyneuritides, coma, or convulsions. This type of toxicity can also be produced by a number of perverted or incomplete organic functions, among which is an excess production of uric acid. All of these act in the cerebro-spinal fluid in which the neurones are bathed. This autointoxication affects the nervous system. It usually establishes a

vicious circle which is constantly enlarging with increasing neuropathological gravity, but is not always reflected by greatly increased uric acid in the cerebro-spinal fluid.

In relation to the child, however, more important than the vicious circle of autointoxication are: (1) The accumulation of the platelets of cholesterol urate on the various circulatory organs, the reduction in their efficiency and the ultimate effect of inhibiting the proper development of the embryo by curtailing its available supply of oxygen. (2) the occurrence of histotoxic anoxia, in which the oxygen supply appears to be normal in every respect, but the degree of oxygen utilization is diminished by the presence of the excess uric acid in the blood and in the cells. The result is an inadequate supply of oxygen for the normal development of the embryo.

Because of the anoxia, the mother responds with a greater respiratory effort for pulmonary ventilation, increased ammonia formation takes place in the kidney, increased acid secretion occurs, there is a general bodily diminution of electrolytes, dehydration results, and the embryo, consequently, is faced with an extreme biochemical environmental change.

It is likely that, in this type of anoxia, the result upon the embryo is an inadequately developed respiratory brain center and circulatory system, since it is a biological corollary that an organism will develop directly in relationship to its externally stimulated environmental need. With the failure of its own respiratory center and circulatory system to develop adequately, general growth disturbing factors become operative and inhibitory action shifts from one organ to another.

The phenomenon of the newborn child with an unusually high uric acid plasma content is indicative of the great quantity of endogenic uric acid produced during pregnancy. Although it has been shown that the rheumatoid pathologies prevail in every age and in both sexes, there is historic proof that the older person is more subject to these degenerative diseases than the younger. This may, in a measure, explain the more frequent occurrence of Mongolism among the children of older mothers.

There is a tendency to attribute many of the infant abnormalities to an etiology involving a recessive gene, but these pathologies are as likely to reflect familial tendencies promoted into active manifestation by similarities of living habits. Of biochemical interest in this

direction is phenylpyruvic oligophrenia which is attributed to genetic inheritance. In light of the fact that special diets with greatly reduced phenylalanine content have given some promise of minimizing the cerebral damage in children with this condition, the question arises as to whether the retardation is caused by the presence of phenylalanine or phenylpyruvic acid, or whether the latter chemical is merely the end product of a metabolic aberration. This has been partially traced by the determination that it involves an enzymatic failure in which phenylalanine is not converted into tryosine. Since phenylpyruvic olegaphrenia is not obvious in the neonatal stage, it may fall into the category of an inhibited development produced by an uncompensated excess of the non-protein nitrogen. In that case, the phenylketonuria would merely be a symptom. In any event, whether genetic or not, the broad, biochemical evidence resolves the pathology to an etiology which must be approached by the clinician from the viewpoint of helping the child by compensating for the shortcomings of its chemical mechanism.

Amaurotic idiocy is another of the degenerative diseases which may be incorrectly attributed to a recessive gene. The fact that it is classed as hereditary because it is most common among Eastern Jews is a questionable premise, since it is not usual to attribute a Mendelian mechanism to a locale or to a race. In light of the fact that, in these cases, the neurons show quantities of stored lipid which may imply accumulated cholesterol esters of high specific gravity, and the fact that the amaurotic idiot was, apparently, healthy at birth, the etiology of this pathology may also lie in one of the uncompensated, metabolic failings of man.

Cerebral Von Gierke's disease similarly shows storage of glycolipids and related materials in the neurons, and results in distressing, degenerative symptoms and death in the first year.

Genetic patterns are also suggested in many of the leukodystrophies which are described as "diffuse sclerosis", but the very nature of the common histological features of these pathologies—free fats, metachromatic glycolipids, cerebrosides, and other abnormal materials—throw into question hereditary explanations and suggest biochemical approaches.

The description, "familial", of some of the leukodystrophies, such as the infantile or Krabbe type, which occur after the first few months, or the Greenfield type, which has its onset in the sec-

ond year, would, perhaps, point to a more accurate etiology, since this terminology may indicate common living habits or similar metabolic problems, rather than direct genetic transmission.

Dystonia Musculorum Deformans, which is also attributed to genetics because it appears, generally, among Russian Jews, hepatolenticular degeneration (Wilson's disease), because familial incidence is common, and the Werdnig-Hoffman syndrome of progressive hypotonia, may also fall into the biochemical patterns transmitted by the mother through metabolic habits, disease, and anoxia, rather than by genetic consequence.

The tendency to uncover genetic continuity based on racial or familial patterns appears to reflect fallacious reasoning, for, by this method of dialectics, we would have deduced that a Mendelian mechanism was manifest in the southerners of the United States in pellagra; in the British Navy in scurvy; in Africans in the sleeping sickness; in the Chinese in beri-beri.

A graphic illustration of this type of faulty deduction is the syndrome, primary degeneration of the corpus callosum, Marchiafava Bignami disease, which occurred among Italians and was thought, until recently, to be genetic. It was finally traced and attributed to the excessive drinking of a particular red wine of the area. It is interesting to note, in relationship to this paper, that red wines, in general, are contraindicated in the gout, rheumatoid-arthritic and related disorders, because of their potential of high uric acid production.

In general, it is difficult for the biochemist or the biologist to classify the unusual child whose abnormalities reflect biochemical influence of a degenerative nature as part of a genetic pattern. It is apparent, in all branches of the science of biology, that biochemical environment is a fundamental factor in the process of development in all stages of life. The habits and customs of race and of family are handed down from generation to generation almost as successfully as the genes carry inherited characteristics. With these habits there comes racial and familial development or degeneration; and, by the evidence of the widespread occurrence of the degenerative and metabolic pathologies, it is, most likely, individual, constitutional factors and environmental adjustment that determine the development of the organisms.

In the devolpment of the child in the prenatal stage, a biochemical change in the environment of the embryo is often indicated by

the development of obscure and indeterminate symptoms in the mother. Hypertension, with no apparent physiological cause, ocular disturbances, labarynthitis, the rheumatoid-arthritis group of pathologies, obesity, hypothyroidism, pseudo-asthmatic symptoms, and skin disorders are often symptomatic evidence that a change is occurring or has occurred in the plasma composition. These changes take a place of importance equal to infectious disease and malnutrition in determining the developmental growth of the child in the foetal stage.

The elevated blood pressure of the mother, which is often felt to be emotional, can be interpreted as a purely functional response to a biochemical condition.

SUMMARY

In the development of the child from the embryonic period to that of pubescence, there has accumulated evidence which indicates that the multitude of abnormalities which may develop can evolve from a purely biochemical etiology. In a manner similar to which the environment of the embryo is affected by inadequate nutrition or disease, biochemical change, due to toxicity or maternal, metabolic error, can affect the ecological conditions of the child and can produce a myriad of congenital malformations.

It can be concluded, generally, that congenital malformation is the result of prenatal pathological processes which have caused an adverse biochemical environment. It follows, therefore, that these abnormalities are not hereditary and occur completely independently of genetic factors.

In the various biological fields of cytology, embryology, teratology, and axial physiological gradients, abnormal development has been noted to occur, primarily, in relationship to the oxidative-reductive processes of the cell. When there is interference with the normalcy of cell respiration, either by reducing the supply of oxygen, by increasing the toxicity of the plasma pool, or by affecting the osmotic quality of the cell membrane, retardation and the development of erotic cell forms take place. By such changes in the biochemical environment of the cell, a staggering number and variety of structural and functional disorders can be produced.

Although these disorders are often attributed to genetic abnormalities of various body proteins or to genetic chemical defects, it is hardly likely that, in the eons of time, in man's evolutionary de-

velopment these errors would not have been eliminated by the law of natural selection. It is more likely that man's dominance in the vertebrate scale and his higher intellect have led him into habits and customs which contribute to the maintenance of the great number of congenital defects.

Despite the devious forms that evolve from malformation and degeneration, it is possible that there exists a common etiology. This common fount of the degenerative diseases, from the prenatal stage to senescence may revolve, to a great extent, about the functioning of cholesterol in relation to the proteins and the non-protein nitrogens. Cholesterol's important function as part of the transport system often becomes affected by an excessive quantity of uric acid with which it forms the ester, cholesterol urate. The body, evidently, cannot handle this compound in large quantities and, when this occurs, the excess is deposited haphazardly throughout the body.

In the fully developed human being, this reaction is manifested by rheumatoid-arthritis pathologies and the atherosclerotic forms, congestive heart condition, and cerebrovascular disease.

In the mother, these accumulations of cholesterol urate affect, adversely, the development of the child.

In the post-natal stages of the child's development, the great amount of uric acid normally present can cause unforeseen difficulties for regular growth. It appears, however, that this large quantity of uric acid is usually adequately controlled by the proteolytic factors of the plasma.

In acute infections, an increase in blood fibrinogen can further complicate the problem of non-protein nitrogen handling by increasing the possibility of the formation of larger, congestive masses with the cholesterol urate. Recently, streptokinase, which has the property of stimulating the formation of fibrolysin, has been used to mitigate the inflammation of this etiology.

The congestion and sclerosis produced by these biochemical problems can occur at any stage of life and is, primarily, dependent on the production and disposal of endogenic and exogenic uric acid. A child who is apparently normal, with no true history of genetic defect, can suddenly slow in its development for a multitude of what may be primary reasons but, actually, may be secondary to a basic biochemical problem rounding about protein metabolism.

Acquired hypothyroidism may result from infection, but is also produced by that broad classification, "unknown causes". Selective or general disturbances of the pituitary may be primary to hypothyroidism, but the deficiency of thyrotropin may be secondary to biochemical change.

Artificial feeding, vitaminization and proteinization appear, from a purely biochemical viewpoint, to increase the problem of non-protein nitrogen handling, producing an unfavorable cell environment for normal development.

The presence of an adequate supply of lactobacilli in the alimentary canal appears to be important for the health of the child. The proper flora for disposal of the non-protein nitrogens which are excreted by the mucous linings appear to be a contributing factor in the proper handling of the uric acid problem.

In the prenatal stage, many of the abnormalities that may occur in the development of the child may be traced to the congestive action of the cholesterol urate complex which may form in the mother. This condition in the mother is usually initiated by hyperuricemia and compounded by the increased levels of cholesterol which normally occurs during pregnancy. In addition to creating conditions conducive to more abundant formation of cholesterol urate, in the older woman the hypercholesteremia produces an elevation in the beta-lipoprotein ratio. This fraction of the plasma lipoprotein has a much higher specific gravity than the alpha form and plays an important role in the etiology of sclerosis. These abnormalities may occur in the mother despite her possession of the estrogenic barriers; for all biochemical relationships are quantitative and depend, primarily, upon the preponderance of one material over the other. The basic effect that this congestion achieves is an interference with the oxidative-reductive process which is the prime instinctive function of the chemical organization of the cell.

An ultimate result of hyperuricemic-induced congestion is histotoxic anoxia. This is reflected in the cell organization by the attempt of the organism to adjust to its new environmental conditions. The cell makes histological adjustments to preserve the oxidative-reductive process and the equilibrium of the chemical organization of the cell. This adjustment produces variations in the development of the respiratory centers and in the circulatory sys-

tem, and results in a general retardation of the developmental process.

CONCLUSION

Although it is unfortunate that, as yet, biochemistry has not advanced to a stage of greater conclusion, it has, nevertheless, presented sufficient evidence to suggest that there should be a reevaluation of the terms: congenital, familial, and hereditary. As long as the unusual child is stigmatized as being purely the product of a Mendelian mechanism, medical thought is straitjacketed by hopelessness in the handling of these abnormalities and all biochemical study, such as presented by this paper, is fruitless.

The fact that the so-called genetically defective child is very often the offspring of normal, healthy parents whose history reveals no genetic defect, opens up large areas of question as to whether the unusual child is truly the result of a recessive, genetic trait or of a biochemical mischance.

The widespread belief that anomalies which occur repeatedly in a family point to heredity is not necessarily correct. The repeated defect in various members of a pedigree does not prove a genetic pattern, since several members of a family may have been exposed to the same pathogenic, environmental factors.

A broad range of illnesses are familial, can be corrected by changes in living habits, and certainly are not hereditary. The over-emphasis on heredity by resorting to the term "mutants" or by explaining away abnormalities by the term "remote recessive" has broad psychological and sociological implications.

To the physician, or to the parent who is confronted with the problem of having children in the face of defects in a first child or a close relative, a determination of familial or biochemical etiology, such as outlined in this work, opens up new avenues of understanding.

To the parent who suffers a guilt or fear complex because of a malformed child, biochemical explanations, such as these, erase erroneous blots from the mind.

Finally, to the clinician and the pediatrician who have been alerted to the biochemistry involved in the etiology of the "unusual" child from conception to pubescence, new opportunities present themselves to compensate, in all of the natal stages, for any

apparent metabolic, environmental cell disadvantages. By avoiding or correcting the hyperuricemic or hypercholesteremic states and their attendant pathologies in the mother, the likelihood of the normalcy of the child is more adequately insured.

By understanding the biochemistry involved in the development of the child, early signals can initiate compensatory or corrective metabolic measures to aid the child toward normalcy. What role the proteolysins, fibrolysins, and phospholipoids play in handling the chemistry involved in the "unusual" child or its mother can only be determined by the clinician and pediatrician in actual practice.

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Annotated Bibliography on Retrolental Fibroplasia*

". . . Your cooperation in forcefully bringing this subject to the attention of your readers will be deeply appreciated by the National Society for the Prevention of Blindness and its Committee on RLF . . ." —John W. Ferree, M. D., Executive Director

PEDIATRICIANS are now fully alerted to the dangers of retrolental fibroplasia from the uncontrolled use of oxygen on premature infants. The following annotated bibliography compiled by the National Association for the Prevention of Blindness in chronological order, shows when it was that knowledge of the cause and prevention of retrolental fibroplasia became available to the medical profession . . . *Editor*

I. Campbell, K.: Intensive oxygen therapy as a possible cause of retrolental fibroplasia: a clinical approach, Med. J. Australia 2:48 (July) 1951.

II. Crosse, V. M., and Evans, P. J.: Prevention of retrolental fibroplasia, A.M.A. Arch. Ophth. 48:83 (July) 1952.

"In our view, supported by the history of the disease in England since 1946, by our own experience, and by comparison with the experiences in other centers in the country, it is right to draw attention to the dangers of the use of too much oxygen and to its administration for too long a period. . . ."

III. Patz, A., and others: Studies on the effect of high oxygen administration in retrolental fibroplasia: I. Nursery observations, Am. J. Ophth. 35:1248 (Sept.) 1952

Study in Gallinger Municipal Hospital, Washington, D. C., was aided by grants from National Institute of Neurological Diseases and Blindness and District of Columbia Society for the Prevention of Blindness. The results of the first of a three-year controlled oxygen nursery study are cited. Authors conclude that there are now sufficient data to question the advisability of the "routine" use of prolonged high oxygen concentrations in the nursery.

IV. Editorial: Retrolental fibroplasia and oxygen, J. Ped. 44:122, 1954.

". . . there is a growing feeling that oxygen should not be given routinely to the premature infant, but reserved for individualized cases of asphyxia and further, it should be used in as low a concentration as possible and for as short a time as possible."

*Commonly abbreviated as RLF

V. Lanman, J. T., and others: Retrolental fibroplasia and oxygen therapy, J.A.M.A. 153:223 (May 15) 1954.

Report of research at Bellevue Hospital, New York, concluding that the authors believed the disease to be directly related to excessive oxygen and felt that it could be controlled by severely restricting oxygen administration to premature infants.

VI. Letourneau, Charles U. Hospitals 28:109 (Aug.) 1954.

The author (assistant director of American Hospital Association and secretary of Association's Council on Professional Practice) stated in this medical review: "We must not allow premature infants to be exposed to high concentration of oxygen routinely. Concentration in cases of emergency up to 40 per cent is allowable, but having prescribed, the physician has discharged his obligation. The rest is up to the hospital to administer the treatment as prescribed. . . . Despite the reading on the flow-meter, the oxygen may not be delivered as the doctor prescribed it. It must be checked by an adequate analyzer . . . The hospital administrator must bear the responsibility for preventing retrolental fibroplasia no less than the physican and the scientist. We have a special part to play in preventing this dreadful disease, and each of us must make certain that he has used all the technical, scientific and professional knowledge available to him."

VII. Hepner, W. R.: Retrolental fibroplasia—Current notes, A.M.A. J. Dis. Child. 88:356 (Sept.) 1954.

On page 359, under heading "Recommendations," the author said: "Oxygen tends to be overused, rather than underused, both in concentration and in duration of therapy. After the first two or three days, concentrations greater than 40 per cent are rarely indicated, and after two or three weeks, need for more than room air is uncommon."

VIII. Nat. Soc. Prev. Blindness: Communication (Oct. 29, 1954) to state and city directors of maternal and child health programs; directors, maternal and child health, schools of public health.

Referred to cooperative research study in 18 hospitals, reported by Kinsey at Symposium on Retrolental Fibroplasia held during October 1954 American Academy of Ophthalmology and Otolaryngology meeting. Consensus of participants, as stated by Algernon B. Reese, M. D., chairman: that routine administration of oxygen to premature babies be discontinued; that it be given only if there be cyanosis or respiratory disease, that in such cases the concentration inside the incubator be kept below 40 per cent as measured by an oxygen analyzer, and that oxygen therapy be discontinued as soon as respiratory distress is relieved. (See reference No. 17)

IX. Rothmund, H. I. M., and others: A field study of retrolental fibroplasia in Maryland, Pediatrics 14:445 (Nov.) 1954.

The authors stated that a recent series of papers by Patz, Ashton, Lanman and others "have indicated that oxygen is an etiologic factor."

X. Abstract of article from Lancet, J.A.M.A. 156:1102 (Nov. 13) 1954.

Reported striking correlation of oxygen administration to premature babies and the occurrence of retrolental fibroplasia.

XI. Editorial, Prematurity, oxygen, and retrolental fibroplasia, J.A.M.A. 157:449 (Jan. 29) 1955.

"In the present state of knowledge, there is certainly no reason to deny small premature infants the benefits of incubator care or of additional oxygen in the amount and duration indicated by relief of cyanosis. And, since retrolental fibroplasia is essentially limited to infants of less than 2,267.9 grm. (5 lb.), there need be no fear of disturbing the eyes of term infants by the oxygen therapy so frequently required for their pulmonary and circulatory disturbances. On the other hand, the evidence is now strong that the exposure of infants to oxygen for even several days is associated with increased incidence of retrolental fibroplasia. Thus, the physician caring for a premature infant should steer a course between preventable anoxia endangering survival on the one hand and the ophthalmologic hazards of unnecessary use of oxygen on the other."

XII. Smith, Clement A.: Oxygen and retrolental fibroplasia, Mod. Hosp. 84:49 (Feb.) 1955.

The author discussed various studies indicating the relationship between oxygen and retrolental fibroplasia, and pointed out that the statistics on the 18-hospitals study reported by Kinsey at a meeting of the American Academy of Ophthalmology and Otolaryngology in September 1954, were highly significant in showing the relationship between prolonged high-oxygen administration and the disease. However, he did not make a strong recommendation as to methods of prevention.

XIII. Editorial, The overuse of oxygen and retrolental fibroplasia, J. Ped. 46:252 (Feb.) 1955.

"If currently available information is disregarded and an infant becomes blind, the burden that lies on the physician and the hospital is unpleasant to contemplate. The conclusion is obvious that discriminate and limited use of oxygen in premature babies is now mandatory."

XIV. Engle, Mary A., and Levine, S. Z.: Response of small premature infants to restriction of supplementary oxygen, A.M.A. J. Dis. Child. 89:316 (Mar.) 1955.

The authors, reporting studies at New York Hospital-Cornell Medical Center, concluded: "There were no detectable late ill effects from the early termination of oxygen administration. It would seem that the administration of oxygen to premature infants of low birth weight as a routine procedure is not necessary."

XV. Lanman, J. T.: The control of oxygen therapy for the prevention of retrolental fibroplasia, J. Ped. 46:365 (Mar.) 1955.

"In summary, the proper control of oxygen use means first its total elimination except for times of clinically demonstrable need. It should then be given for as brief a time as possible at concentrations below 40 per cent." The author then went on to say how to control the concentration.

XVI. Kinsey, V. E.: Letter to the editor, Pediatrics 18:511 (Sept.) 1956.

"In view of the positive evidence indicating that even relatively short exposures to oxygen are associated with RLF, even though the concentration is kept below 40%, and the paucity of evidence that there is any critical concentration below which RLF is markedly reduced in incidence, I believe that merely restricting the concentration of oxygen, without stringently reducing the duration in oxygen, may result in unnecessary cases of RLF. Certainly, the emphasis should be placed on restricting the duration in oxygen to an absolute minimum consistent with the clinical indications of anoxia irrespective of the concentration of oxygen administered."

XVII. Kinsey, V. Everett, and others: Retrolental fibroplasia—Cooperative study of retrolental fibroplasia and the use of oxygen, A.M.A. Arch. Ophthal. 56:481 (Oct.) 1956.

The authors' recommendations: "The length of time a premature infant, particularly an infant of multiple birth, is kept in an environment containing oxygen in concentrations in excess of that of air should be kept to an absolute minimum, consistent with the clinical indications of anoxia. When oxygen therapy is clearly required, it should be prescribed on an hourly basis and the concentration should be as low as possible."

XVIII. Patz, Arnall: The role of oxygen in retrolental fibroplasia—E. Mead Johnson award address, Pediatrics 19:504 (Mar.) 1957.

"These clinical and experimental data justify recommendations for a rigid supervision of oxygen administration to the premature infant to avoid any unnecessary overuse of this potentially toxic agent."

The above bibliography is by no means a complete listing of the articles that have been published on this subject. It does indicate that numerous articles were in the literature pertaining to the role of oxygen in the etiology of RLF.

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Average adult dose: 250 mg. four times a day. Pediatric dosage: 22-25 mg./Kg. (10-11.5 mg./lb.) body weight daily in 4 divided doses. Each dose should be taken with meals, and with food or milk at bedtime. *Alcohol should not be ingested in any form, medicinal or beverage, during* ALTAFUR *therapy and for one week thereafter.*

*Based on a projection of ALTAFUR Tablets dispensed in 10 months since their introduction.

†Compiled by the Medical Department, Eaton Laboratories, from case histories received.

NITROFURANS—a *unique* class of antimicrobials

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